

38. A method for stimulating mucosal immunity, comprising nasal administration to a subject in need thereof a composition comprising a recombinant protein encoded by the recombinant DNA of claim 1.--

REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised to define the invention with additional clarity (claims 23-25, 32 and 33 have been cancelled). Support for the revisions, and for the newly presented claims, can be found throughout the disclosure. That the claims have been revised should not be construed as an indication that Applicants agree with any view expressed by the Examiner. Rather, the revisions are made merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

The Examiner's comments regarding the drawings are noted. Formal drawings will be submitted when this case is otherwise in condition for allowance.

Claims 1-5, 7, 10, 12-21, and 27-30 stand rejected under 35 USC 103 as allegedly being unpatentable by Menozzi et al. Withdrawal of the rejection is submitted to be in order in view

of the above-noted claim revisions, offered for purposes of clarity, and in view of the comments that follow.

Menzio et al report a fundamental study of the binding properties of Fha. For practical purposes only, i.e., to facilitate the purification of Fha fragments (see page 774, left column, last paragraph), some fusions were made between a portion of Fha and the maltose-binding protein (MalE). However, the MalE protein exhibits only the property of binding to the maltose molecule and there is no indication in that article that any molecule fused to Fha would retain any biological activity. Moreover, MalE protein expression is exclusively intracytoplasmic: as a matter of fact, the secretion is efficient only if a signal sequence exists on the N-terminal part of the protein. This is not the case in Menozzi et al, wherein the Fha moiety containing a signal sequence in its N-terminal part is fused to the C-terminal extremity of MalE; thus, the signal sequence of Fha is in the middle of the MalE-Fha fusion protein which likely renders this secretion sequence inefficient.

In contrast, and in accordance with the present invention, biologically active polypeptides are fused to portions of Fha, the resulting fusion protein is secreted or exposed at the cell surface, and the biologically active polypeptide is functional both *in vitro* and *in vivo*. There would have been no suggestion in Menozzi et al of the present invention (that is, there would

have been nothing to motivate one skilled in the art to prepare the instantly claimed constructs). Even if such motivation had existed, which Applicants deny, there would have been no basis for reasonably expecting that the advantageous properties associated with the present invention, such as high immunogenic activity, mucosal immune response, nasal administration, etc., could be achieved

As the claimed recombinant DNA for the expression of highly immunogenic fusion proteins would not have been suggested by the cited art, reconsideration is requested.

Claims 6, 8 and 9 stand rejected under 35 USC 103 as allegedly being obvious over Menozzi et al and Delisse-Gathoye et al. The rejection is traversed for the reasons that follow.

Menozzi et al, as stated above, does not disclose or nor would it have suggested highly immunogenic fusion proteins.

It is submitted that Delisse-Gathoye et al would not have remedied the deficiencies of the primary reference. Indeed, as correctly pointed by the Examiner, Delisse-Gathoye et al reports the existence of highly homologous regions in the N-terminal domains of Fha Sh1A and HpmA, but this article, neither alone nor in combination with Menozzi et al, would have provided the skilled artisan with any reasonable expectation that such chimeric proteins would exhibit high immunogenic activity *in vitro* and *in vivo* and, in particular, high mucosal immunogenic activity.

Moreover, in the present invention, the antigenicity is conferred by the non Fha fused moiety of the chimeric protein.

Withdrawal of the rejection is respectfully requested.

Claims 32 and 33 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. These claims have been cancelled and Applicants submit that newly added claims 35-38 should render this rejection moot.

Claim 7 has been amended as well and it is earnestly believed that the claim as revised makes clear that which Applicants intend.

Reconsideration is requested.

Claims 11 and 31 (now 11 and 32) stand rejected under 35 USC 103 as allegedly being obvious over Menozzi et al in view of Relman et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Menozzi et al, as discussed extensively above, teaches fusion proteins that do not exhibit any immunological activity.

Relman et al teaches the expression of Fha from various hosts and suggests that Fha can be combined or mixed with other proteins where immune response to more than one antigen is desired. This approach is quite different from the present invention.

In the present invention, the Fha fragment fused to the antigen is used as a "vector" to facilitate the presentation of

the antigen encoded by the heterologous sequence (1) to the immune system, and particularly to the mucosal immune system. This concept would not have been suggested by Relman et al, where the co-expression of another antigen with Fha is proposed only to elicit an immune response against both antigens, not to achieve a particular presentation of this antigen.

It is respectfully submitted that Relman et al, neither alone nor in combination with Menozzi et al, would have provided the skilled artisan with any motivation to make the chimeric proteins of the present claims in order to obtain high mucosal immunogenicity activity. Withdrawal of the rejection is therefore respectfully requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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